

EPIDEMIOLOGY OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Harold S. Novey, MD

Shortly after Hinson et al proposed the term *allergic bronchopulmonary aspergillosis* (ABPA) in 1952,²³ Pepys et al at the Brompton Hospital, London, discovered several immunoserological features that confirmed the designation of allergy.^{30, 31} The initial proposal was based on only three patients: two women ages 45 and 55 years and a 37-year-old man. Their criteria for the diagnosis of ABPA were as follows: recurrent fever, radiologic evidence of recurrent collapse and consolidation in different areas; sputum containing "plugs" from which fungi could be cultured (all three had *Aspergillus fumigatus*); and a blood eosinophilia of 1000/mm³. Interestingly, neither asthma nor bronchiectasis were considered diagnostic criteria, although each patient had evidence of asthma, and two had definite saccular bronchiectasis whose location, central or peripheral, was not emphasized. Hinson et al thought sensitization to the fungus was the pathogenic mechanism because of the eosinophilia, character of the sputum, and absence of significant fungal invasion in histologic examinations of biopsy and necropsy material. They attributed inconclusive results of skin tests to *Aspergillus* extracts in two of the patients and controls to the quality of the extracts.

It remained for the Pepys group to develop fungal extracts that produced immediate and delayed skin tests and serum precipitating antibodies that showed clinical correlation. By 1971, they had published a series of 111 cases diagnosed as ABPA and proposed the immunopathogenic mechanism of a combination of IgE-mediated (Gell and Coombs

From the Division of Basic and Clinical Immunology, Department of Medicine, University of California, Irvine, Orange, California

Type I) and immune complex-mediated (Type III) factors.³⁰ Bronchiectasis of a central or proximal distribution was considered a complication of recurring local bronchial plugging and resultant immunologic inflammation. For the first 16 years after the initial report, it was believed to be a disease limited to the United Kingdom. Eventually, reports first by Patterson and Golbert⁴¹ and then by Slavin et al⁵¹ conceded it was present in North America but only as a rarity. By 1973, however, ABPA was termed no longer rare in the United States,²⁴ probably because of the more widespread application of potent *Aspergillus* extracts in both in vivo and in vitro tests and heightened awareness; the diagnosis was being reported worldwide.⁴³

The true prevalence of ABPA remains highly speculative: ABPA is not recognized in the international classification of diseases (including the ninth revision of 1996) and the diagnostic criteria lack clinical uniformity and standardized tests. Thus epidemiologic conclusions will be based on circuitous reasoning. In this article, an attempt is made to approach its prevalence by several routes. Statistical and epidemiological aspects of related or associated diseases such as asthma, cystic fibrosis, bronchiectasis, pulmonary eosinophilia, and aspergillosis are invoked. Sensitization rates to *Aspergillus* antigens are also assessed. Finally, we discuss whether ABPA represents a condition recently born or recently discovered.

PREVALENCE OF ABPA

There have been several preliminary efforts to determine the prevalence of ABPA in the United States. A report in 1983² uncovered 352 cases by surveying institutions that served as diagnostic centers. Geographically, the sources were predominantly in the Midwest and southern California.

In 1990, the author distributed a brief questionnaire to each board-certified pulmonologist and allergist in Orange County, California, population 2.4 million. Of the 72 specialists sampled, 54 replies were received (75%), 30 from the pulmonologists, and the remaining 24 from allergists. Results are seen in Table 1. An assumption was made that most con-

Table 1. PREVALENCE OF ABPA IN ORANGE COUNTY, CALIFORNIA, 1990—BY SPECIALTY

	Pulmonary (30 Respondents)	Allergy (24 Respondents)
ABPA patients under current care	14	10
ABPA patients ever seen	83	60
Most per respondent under current care	3	4
Most per respondent ever seen	12	5

firmed cases of ABPA would have been examined by a pulmonary or allergy specialist. A total of 24 cases were acknowledged at this single sampling. Assuming all 72 specialists responded with the same rate of discovery, an additional 8 ABPA patients, or a total of 32 patients, would be under current care. Over their practice lifetimes, they had observed a total of 143 cases. No specialist had more than 4 ABPA patients under current care or had ever seen more than 12. Counting overlapping consultations, it is likely there were less than 143 different patients. Another assumption, unverified, is that the respondents correctly diagnosed their cases and reported the numbers accurately.

The newly formed ABPA Committee of the American Academy of Allergy, Asthma and Immunology (AAAAI), in a move to establish a national registry of ABPA patients, surveyed the membership of the Academy in 1991. A response rate of 33% yielded 1038 replies to the requests shown in Table 2. A total of 703 patients with ABPA were under current care, nearly half (49%) of whom were shared with other physicians. Again, if the same case rate were present among the nonrespondents to the survey, the total cases by all Academy members would total about 2000 patients. It must be acknowledged that this survey did not establish the accuracy of the rest of the data, so that the replies essentially represent allergists' perceptions. As also shown in Table 2, diagnostic criteria applied by the respondents were quite variable.

Extrapolated from the Orange County, California, survey, there were 1.25 as many pulmonary as allergy specialists. The pulmonologists had 1.4 times the number of ABPA patients as the allergists. The 2000 theoretic patients of the Academy members would be supplemented by 3500 patients under care by pulmonologists, assuming no shared cases, for a total of 5500 ABPA patients diagnosed by the two specialty groups. The Orange County cases would translate to a nationwide total of 3200 patients on the basis of a 1:100 population ratio. Even more speculation is needed to estimate the number of ABPA patients not examined by one of the specialists. If one simply doubles the number of ABPA patients not diagnosed by specialists, there would be somewhere between 7000 (Orange County figures) and 11,000 (Academy survey) patients with ABPA in the United States. Unexplained are the whereabouts of all the previously observed patients not currently under care. Mortality data is against large death rates from the disease itself, so that the majority of deaths would be caused by conditions other than ABPA. Some ABPA patients may be in remission and no longer under physician oversight. The remainder must be considered as being managed by nonrespiratory specialists. However, the marked decline of cumulative patients currently under specialist supervision also suggests a decrease in new case discovery. The projected maximum 11,000 patients with ABPA represents less than 1% of the estimated 12 million asthma patients in the United States. However, because cystic fibrosis (CF), not asthma per se, could be the underlying disease, the rate of ABPA per asthma patient would remain well under 1%. The 11,000 patient estimate

Table 2. ABPA SURVEY (AAAAI COMMITTEE ON ABPA, 1991)

Part I		Part II	
Request: List number of patients diagnosed as ABPA under your care currently		Request: List number shared with another M.D., and diagnostic specialty	Request: List number treated in past
Total currently under care	703	Total shared with another M.D.	Total treated in past
Average per respondent	1	Pulmonary	Average per respondent
Average with at least one patient	29	Internal medicine	Average with at least one patient
Smallest number per respondent	0	Allergy/immunology	Largest number per respondent
		Pediatrics	Smallest number per respondent
		Family practice	
		Cystic fibrosis	
		Others	
			2200
			2
			53
			100
			0

Part III	
Request: List criteria used in diagnosis of ABPA patients	
Historical features	871
Skin tests	930
Immediate	813
Late	328
Serology	802
Total IgE	875
Specific IgE	575
Precipitins	699
Specific IgG	446
Eosinophilia	641
Radiologic	559
Plain film	545
CT scan	170

for ABPA in the United States with a population of 260 million is equivalent to one ABPA patient per 24,000 population.

PREVALENCE OF SENSITIZATION TO *ASPERGILLUS*

Another approach to estimating the prevalence of ABPA is to determine groups at risk. Sensitization rates to *Aspergillus* antigens would define one such group.²⁶ Fortunately, there exists a substantial amount of published data regarding immediate skin sensitivity to *Aspergillus* extracts. There is a surprising degree of unanimity about these rates among several groupings (Table 3), especially surprising in view of the disparity of reactivity found by Howard Schwartz⁴⁴ among five commercially available *A. fumigatus* extracts. For example, among the total of 1794 mostly adult individuals with asthma listed in Table 3, the range of positive epicutaneous tests was 13% to 38%, or an average of about 25%. This range used the 3 mm wheal figure in the South African study. The largest diversion from this range was the 2% rate among Thailand patients, but they were all under 17 years of age²⁷ and were excluded from the above estimate. The percentage of asthma patients with a positive skin reaction to an *Aspergillus* extract would be slightly increased if intracutaneous tests were included, as judged from the Montreal rate of 39% positive.

There are few data from normal subjects, but among nonasthmatic atopic patients there were rates of 17, 31, and 40% for the total 776

Table 3. PREVALENCE OF IMMEDIATE SKIN SENSITIVITY TO *ASPERGILLUS* EXTRACTS

Location	Population (Number and Type)	<i>Aspergillus</i> Extracts (Number)	Percentage Positive (Epicutaneous)	Percentage Positive (Intracutaneous)
Canada (Montreal)	200 asthma	2	21.5	39
USA (St. Louis)	379 atopic	1	17	ND
S. Africa (Cape Town)	500 chronic asthma, 50% steroid dependent	3	26 (3 mm wheal) 44 (2 mm wheal)	ND
UK (Bristol)	238 asthma	1	38	ND
UK (London)	656 asthma	2	13	ND
USA (Cleveland)	100 asthma	1	28	ND
UK (London)	100 asthma	1	23	ND
USA (North Carolina)	87 CF	1	ND	47
USA (St. Louis)	112 CF	1	42	ND
USA (Seattle)	51 CF	2	16	14
Thailand	100 asthma (<17 yrs)	1	2	ND
USA (California)	271 atopics	Variable	Combined	40
USA (California)	126 atopics	Variable	Combined	31
UK (Manchester)	30 CF	4	50	ND
UK (London)	43 CF	1	58	23
UK (Birmingham)	48 CF	1	35	ND

ND = Not done; CF = cystic fibrosis.

Table 4. PREVALENCE OF SERUM PRECIPITINS TO *ASPERGILLUS* EXTRACTS

Location	Population (Number and Type)	<i>Aspergillus</i> Extracts (Number)	Percent Positive	Date and Reference Number
UK (London)	75 normal	1	3	1967 ³⁵
USA (California)	117 normal	7	2	1979 ⁴⁰
UK (London)	60 asthma	1	7	1967 ³⁵
Canada (Montreal)	200 asthma	6*	22.5	1981 ³¹
USA (California)	795 respiratory symptoms	7	18	1979 ⁴⁰
UK (Oxford)	98 respiratory distress	4†	51	1992 ¹⁷
UK (London)	51 normal and atopic	4†	6	1977 ³²
UK (London)	112 CF	1	31	1967 ⁹
UK (London)	37 CF	1	27	1969 ³¹
UK (Manchester)	43 CF	1	37	1975 ³
USA (Cleveland)	141 CF	1	31	1970 ⁴⁷
USA (California)	22 CF	6	59	1976 ¹⁹
USA (New York)	46 CF	4*	37	1979 ³⁸

*Commercial.

†Others prepared by research labs except 1 of 4.

persons tested (see Table 3). The higher rates included the addition of intracutaneous test results. For patients with CF, there was a generally higher rate. The range varied from 35% to 81%; the higher rates included both skin test procedures (see Table 3). The average sensitization rate among these CF patients was 50%. Thus about 25% of adults with asthma, 30% of atopics without asthma, and up to 50% of CF patients developed evidence of IgE antibodies to mostly crude commercially available extracts.

Data also exist for the rate of serum precipitating antibodies among similar groups (Table 4). These antibodies, mostly belonging to the IgG class, but containing some IgA and IgM types, are referred to as precipitins. The range of positivity is 27% to 59% (average 37%) for the group of 401 CF patients. Most of the antigens, in contrast to the extracts used in the in vivo tests, were prepared in the various research laboratories. The higher rates of reaction involved the application of up to seven different extracts. For 60 patients with asthma, only 7% had precipitins, whereas the 795 patients with various pulmonary conditions that may have included those with ABPA had an 18% rate for precipitins. Among 243 supposedly normal controls, under 7% had precipitins.

Assuming that both IgE and precipitin antibodies to *Aspergillus* antigens are required to diagnose ABPA, further extrapolations can be made from the data. If 3% of well persons and 18% of those with respiratory diseases have serum precipitins, then 15% (18 - 3) of asthmatics may have precipitins associated with disease states. Projecting a rate of 25% for IgE antibodies to *Aspergillus* among 12 million with asthma, which equals about 4 million, then about 15% of these, or 450,000 could be projected to be at risk for both IgE and precipitins to *Aspergillus* and thus candidates for ABPA. Of course, among CF patients the risk rate would approach 48%.

PREVALENCE OF DEATHS AND HOSPITALIZATIONS FROM RELATED CONDITIONS

How many patients die from ABPA in the United States annually? Relatively few, judging from data available from the National Center for Health Statistics. Deaths from bronchiectasis totalled 950 in 1992. Total deaths combined from pneumonia in aspergillosis and from pulmonary eosinophilia in 1992 were 649. Most of these latter deaths were likely caused by invasive aspergillosis and hypereosinophilic syndromes rather than ABPA. This conclusion is supported by the multicause retrieval data (Table 5) that produced only seven deaths from aspergillosis and bronchiectasis, and aspergillosis and pulmonary eosinophilia. As for CF, even if a substantial percent died from complications of ABPA, there were only 397 deaths reported in 1992 caused by CF.

Perhaps a significant portion of the over 4,000 deaths from asthma were caused by ABPA. Again, the multicause retrieval data do not support ABPA as an important contributory factor in asthma deaths. There were 28 deaths from asthma with bronchiectasis, two from asthma with pulmonary eosinophilia, and seven from asthma and aspergillosis. These 37 deaths are candidates for ABPA, but they still represent under 1% of all asthma deaths (0.8%) annually.

Hospitalization for ABPA would also not appear to be substantial. Of the 1,053,000 patients discharged with asthma as a primary diagnosis in 1994, a maximum of 58,000 (5.59%) have had evidence of either bronchiectasis, pulmonary eosinophilia, pneumonia in aspergillosis, or aspergillosis according to data obtained from the National Center for Health Statistics. It is unlikely that ABPA was the actual cause for most of these hospital diagnoses.

PREVALENCE OF ABPA IN ASTHMA

When Schwartz and Greenberger⁴⁶ studied 100 patients with asthma in Cleveland who had been found to have a positive skin-prick test to *A. fumigatus*, they uncovered evidence of ABPA at least serologically in 28. Of these, 10 also had radiographic evidence of central bronchiectasis. In another group of 531 patients with asthma and immediate cutaneous

Table 5. MULTICAUSE MORTALITY DATA RETRIEVAL*

Disease Combinations	Deaths
Asthma and aspergillosis	7
Asthma and pulmonary eosinophilia	2
Asthma and bronchiectasis	28
Aspergillosis and bronchiectasis	6
Aspergillosis and pulmonary eosinophilia	1

*Data from the Centers for Disease Control and Prevention, US Department of Health and Human Services, Atlanta, GA, 1987.

reactions to *Aspergillus* extracts, Greenberger and Patterson²⁰ diagnosed 3.6% with ABPA and central bronchiectasis. Among steroid-dependent asthmatics, 3 of 42 or 7% had definitive ABPA, and another 3 had less convincing evidence.⁷

Earlier, estimates of 8% to 11%²¹ prevalence of definite ABPA among patients with asthma were made in the United Kingdom by several groups between 1959 and 1968. Probable ABPA, based on varying diagnostic criteria, was suspected in upwards of 22% of selected asthma populations. In 1971, an Australian group reported on a screening of 250 patients for ABPA in their chest clinic.¹ Nearly 10% had various combinations of their five criteria required for a confirmed diagnosis, but none had all. These studies highlight the difficulty in determining prevalence of a condition in which diagnostic criteria are not established. Even central bronchiectasis may not be pathognomonic of ABPA. Computed tomographic scanning of the lungs of 11 patients with asthma and cutaneous reactivity to *A. fumigatus* but without other criteria of ABPA yielded evidence of bronchiectasis in 2 versus 14 of 17 patients diagnosed with asthma and ABPA.⁴ Bronchial dilation and pleural thickening were more widespread and severe in the ABPA asthma group. Of 102 lobes studied in the ABPA patients, evidence of bronchiectasis was present in 43, in contrast with 3 of 66 lobes in the non-ABPA asthma patients.

PREVALENCE OF ABPA IN CF

Although ABPA was first described in association with asthma, there appear to be more published studies of its incidence among CF patients. Since the report by Mearns et al in 1965³⁶ of two CF patients with ABPA, a relatively common occurrence of ABPA in CF has been reported. Most studies required the findings of radiologic evidence of recurrent pulmonary infiltrates, blood eosinophilia, sputum containing *Aspergilli*, and the presence of specific IgE and precipitins to *Aspergillus* extracts to diagnose ABPA in their CF patients. In London Batten⁹ found five cases of ABPA, ages 8 to 29 years, among 180 CF patients, a 3% rate. Also in England, over a 3-year period, 6% of 137 CF patients were diagnosed with ABPA by Simmonds et al.⁴⁸ In upstate New York, Nelson et al³⁸ found five cases of ABPA among 46 CF patients, or 11%, over a 2-year period; in the Midwest, 10% of 100 CF patients had features indicative of ABPA.²⁸ In more recent studies during this decade, an incidence of 8.6% of 105 CF patients in England,³⁹ 5.4% of 147 CF patients in one series,¹⁶ and 6.4% of 236 CF patients in another series in the southeastern United States³⁷ were considered to have ABPA. Using stringent criteria, Hutcheson et al in St. Louis²⁵ could find only 6 of 118 CF patients with ABPA. Others in the group with partial parameters for ABPA were shown to experience spontaneous changes in five immune markers over a 12-year observation period. The authors concluded that it was not possible by their tests to predict who would eventually

develop ABPA. Generally, the children with ABPA were diagnosed at an age somewhat older than the mean for the entire group, around age 14. They also had a higher incidence of atopy and asthma, and more severe disease than other CF patients. Two studies correlated increased severity with increased *Aspergillus* precipitin activity.^{19, 35}

Thus, despite differences in diagnostic criteria, *Aspergillus* extracts, laboratory methodology, demographic and geographic features, the incidence of ABPA among mostly children with CF falls within a relatively narrow range of 3% to 11%. The average incidence is approximately 7% for ABPA among the total of 1069 patients with CF in the eight studies cited in this section.^{9, 16, 25, 28, 37, 38, 39}

PREVALENCE OF *ASPERGILLUS* ORGANISMS IN THE ENVIRONMENT

Nearly all studies of air sampling for *Aspergillus* spores place this organism in the first 15 of frequency among fungi, whether indoors or outdoors. There is an increased predilection for higher humidity, rainier areas, and during fall and winter months in some surveys.²⁶ Bardana, in a comprehensive review in 1980, noted that 94 worldwide surveys found *Aspergillus* species represented between 0.1% and 22% of total air spora sampled.⁵

Sinski⁴⁹ estimated that an active man could inhale a total of 5.7×10^7 spores of all types in 24 hours. If, however, he were working in a barn with hay and grasses, he would likely inhale 8.4×10^7 spores in only 3 hours with upwards of 82% generated by *Aspergillus* and *Mucor* species. Human sputum and lung cultures have revealed consistent isolates of *Aspergillus*, second only to *Candida*.⁶ Owing to its spore size and spherical shape (average 2.5μ), *Aspergilli* were found in higher portions in lung than sputum samples.⁸ Since its natural habitat is decaying vegetation, it is unlikely that *Aspergilli* are more common in today's industrial environment than during the agricultural eras. Thus, increased human exposure to the fungi would not serve to explain the increased recognition in disease. Most case reports of ABPA do not equate the condition with undue exposure and assume it is due to the ubiquitous nature of the organism.^{43, 54} It is noteworthy, however, that the three original cases cited were associated with gardening, farming, and baking. In this author's experience, many of his confirmed ABPA patients were subjected to excessive exposure, such as plumbing leaks, indoor flooding, compost piles, and hay-containing barns and horse corrals.⁴⁰ There have also been reports that inhaling contaminated *Cannabis*-containing cigarettes have contributed to the disease.²⁹

DID ABPA EXIST BEFORE 1952?

It is difficult to explain why the triad of asthma, bronchiectasis, and *Aspergillus* was not recognized until 1952, when each separately or in

pairings were known for many prior years. A relationship between asthma and bronchiectasis was reported frequently, especially prior to the introduction of antibiotics. Feinberg found bronchographic evidence of bronchiectasis in 14 of 50 consecutive patients with asthma.¹⁸ Among another series of 110 patients with bronchiectasis, four also had asthma, and their bronchiectasis was classified as cylindrical. There was no mention of location or the presence of fungi.¹⁴ A report⁵⁶ from a Tucson, Arizona clinic classified 90% of their bronchiectasis patients (number not given) as allergic based on 10% or more eosinophils in their bronchial secretions and associated allergic diseases. In a recent review article,⁵⁷ Zhaoming and Lockey cite evidence for case reports as far back as 1936 that resembled ABPA.

Fungal spores were considered provoking factors for asthma in Blackley's studies in 1873, and fungal antigens including *Aspergillus* species have been employed in diagnostic tests for allergy at least since 1924.¹² *Aspergilli* have been reported as a predisposing factor in bronchiectasis, along with a host of other diseases.⁴⁹ The organism was discovered and named by Micheli, the monk-botanist, in 1729, from its germinating appearance to the brush, or aspergillum, he used in sprinkling holy water during high mass. Definitive diagnosis of *Aspergillus* pulmonary infections began in 1847, so that its relation with human pulmonary disease, and with asthma, had been documented over 50 years before Hinson et al's discovery.⁵

Additionally, human exposure to the fungus has likely decreased rather than increased during this time, as discussed earlier. One can only speculate that ABPA probably predated its recognition and does not represent a newborn disease.

CONCLUSION

If indeed ABPA is a distinct clinical entity, its prevalence will not be known until several standards are met. Resolutions of the concepts ABPA-serological and ABPA as a distinctive disease with the presence of peri- or extrabronchial pathology must be made in all published reports and surveys.⁵³ Standardized diagnostic criteria and laboratory tests are essential. Such standards should encourage inclusion into the international classification of diseases and thereby provide more reliable statistical data.

Our best understanding of its prevalence under existing limitations suggests that ABPA could be present in between 0.25% and 0.8% of all asthma patients in the United States. In specific surveys, only 703 current cases were diagnosed by about 1000 allergists in 1991 and 352 cumulative cases among 7 medical centers prior to 1983. In these surveys, patients with underlying asthma and CF were combined. Criteria for diagnosis of ABPA in CF is perhaps even more hazardous in view of preexisting bronchopulmonary pathology and infection. Extrapolations from published studies suggest a rate of no more than 11% and closer

to 7% for ABPA in CF. Although life-threatening complications such as pulmonary fibrosis and bronchocentric granulomatosis have been attributed to ABPA, mortalities directly related to the condition appear to be exceedingly rare. Acceptable conclusions, not only about prevalence but also about management and prognosis, are elusive without a standard of diagnosis for ABPA.

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Address reprints requests to

Harold S. Novey, MD
 Division of Basic and Clinical Immunology
 Department of Medicine
 University of California, Irvine
 Building 53, Route 81
 101 The City Drive South
 Orange, CA 92868

e-mail: hsnovey@uci.edu

